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Chem. Sci., 2011,2, 2326-2331 DOI: 10.1039/C1SC00521A

Enantioselective rhodium-catalyzed arylation of electron-deficient alkenylarenes†

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DOI: 10.1039/C1SC00521A

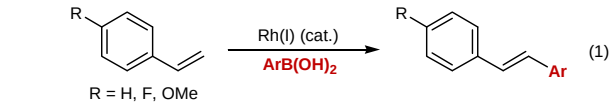
β-Substituted alkenyl-*para*-nitroarenes, an unexplored substrate class for catalytic asymmetric addition reactions, undergo highly enantioselective rhodium-catalyzed arylations with arylboronic acids in the presence of a dibenzylamide-containing chiral diene ligand. One example of asymmetric arylation of an alkenyl-*p*-cyano-*m*-(trifluoromethyl)benzene is also presented.

Catalytic enantioselective additions of organometallic reagents to activated alkenes are an important class of reactions for the production of enantioenriched chiral compounds.[1] However, examples of such processes where alkenes are activated by arenes or heteroarenes are uncommon, presumably due to the relatively low levels of activation that (hetero)arenes provide. Given the ubiquitous nature of (hetero)arenes in compounds for applications ranging from biology to materials science, the development of reactions that address this deficiency is highly desirable.

Our group has demonstrated that heteroarenes containing a suitably placed C=N moiety are able to activate alkenes[2] towards enantioselective copper-catalyzed reductions[3] and rhodium-catalyzed arylations,[4] while Bernadi, Adamo, and co-workers have developed asymmetric additions of nitroalkanes to 4-nitro-5-styrylisoxazoles.[5] For alkenes conjugated to simple arenes (which in general provide only minimal activation), highly reactive organometallic reagents are usually required.[6] A number of groups have reported stoichiometric or catalytic enantioselective carbolithiations[7,8] of various alkenylarenes[9,10,11] mediated by (–)-sparteine[9,10] or a (+)-sparteine surrogate.[11] Although these carbolithiations work well, the development of processes that proceed under milder conditions, employing organometallic reagents that exhibit greater functional group compatibility, represents an unmet need. In this paper, the catalytic enantioselective addition of arylboronic acids to alkenes conjugated to electron-deficient arenes is described.

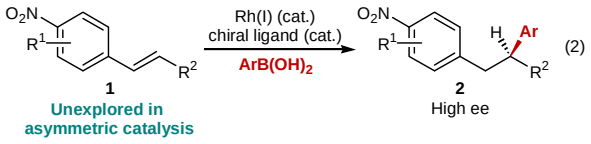
The rhodium-catalyzed asymmetric 1,4-addition of arylboron compounds to β-substituted electron-deficient alkenes is now a well-established method for the preparation of chiral compounds.[12,13,14] Since the initial discovery of enones as substrates for these reactions,[12] subsequent efforts have extended the scope of the acceptor[15] to alkenes conjugated to a range of common electron-withdrawing groups.[16,17,18,19,20,21,22] More recently, less common activating groups have been employed. In addition to our report of asymmetric arylations of alkenylheteroarenes,[4] which builds upon work by Lautens and co-workers describing non-enantioselective additions of boronic acids to vinylazines,[23] Sasaki and Hayashi have disclosed the asymmetric arylation of borylalkenes.[24] However, rhodium-catalyzed addition of arylboron compounds to alkenylarenes has not, to our knowledge, been described. Instead, simple styrenes (where activation of the alkene is minimal) were shown by the Lautens group to undergo Heck-type reactions under aqueous conditions using water-soluble phosphine ligands (eq 1).[23]

Ref. 23:



(1)

This work:



(2)

It occurred to us that placement of the strongly electron-withdrawing nitro group at the *para*-position of the arene might lead to sufficient polarization of the alkene to the point where addition products **2**, rather than Heck-type products, would form, even for 1,2-disubstituted alkenes (eq 2). Although nitroalkenes have been successfully employed in myriad additions of carbon nucleophiles,[19,25] the analogous reactions of their phenylogous counterparts **1** are extremely rare,[6c–h] and no asymmetric reactions have been reported. Therefore, the successful realization of the reactions depicted in eq 2 was an attractive goal, and would set the stage for the use of this underexploited class of electrophiles in other catalytic enantioselective addition reactions.

Our initial experiments focused upon alkenyl-*p*-nitroarene **1a**

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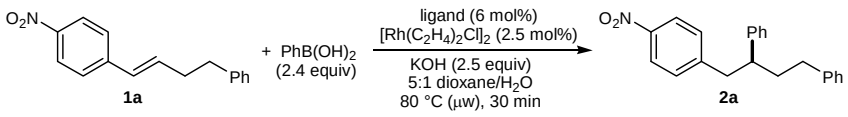
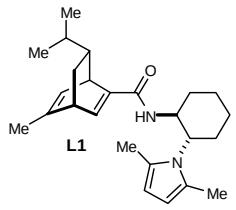
† Dedicated to the memory of Hamish McNab. Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data for new compounds, and crystallographic data in cif format. CCDC reference number 809081. See DOI: 10.1039/c1sc00521a

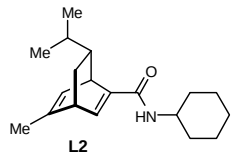
Table 1 Ligand optimization for the asymmetric arylation of **1a**[a]



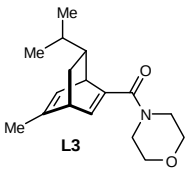
Ligands:



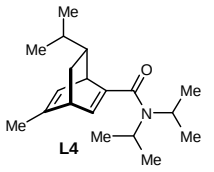
L1



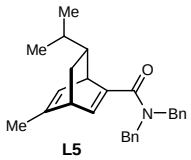
L2



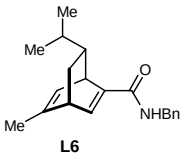
L3



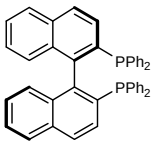
L4



L5



L6



(*R*)-BINAP (**L7**)

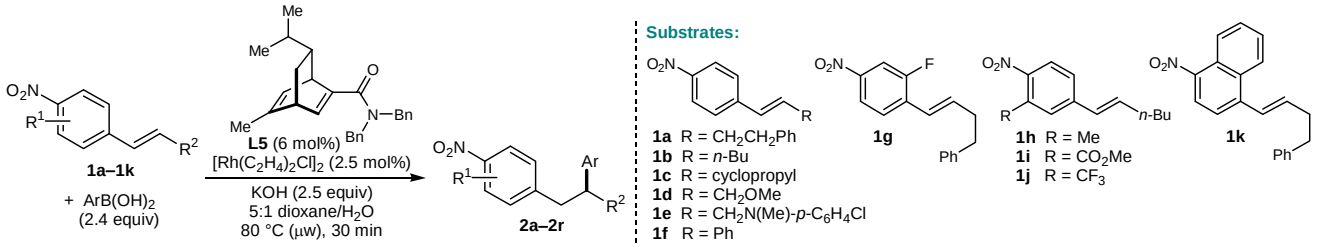
Entry	Ligand	Conversion (%)[b]	ee (%)[c]
1	—[d]	42	n/a
2	**L1**	35	97
3[e]	**L1**	70	95
4	**L2**	24	95
5	**L3**	76	70
6	**L4**	84	87
7	**L5**	>95[f]	95
8	**L6**	44	90
9	**L7**	66	97

[a] Reactions were conducted using 0.20 mmol of **1a** in dioxane (0.5 mL) and H_2O (0.1 mL). [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $[Rh(cod)Cl]_2$ was used in place of $[Rh(C_2H_4)_2Cl]_2$, without an additional chiral ligand. [e] Reaction conducted at 120 °C for 30 min. [f] Product **2a** was isolated in 92% yield.

as a test substrate (Table 1). As a preliminary gauge of reactivity, the addition of $PhB(OH)_2$ to **1a** was performed using $[Rh(cod)Cl]_2$ (2.5 mol%) and KOH (2.5 equiv) in dioxane/H_2O at 80 °C under microwave (μw) irradiation[26] for 30 min. This experiment resulted in 42% conversion into *rac*-**2a** (entry 1). Next, the use of chiral ligands were evaluated in combination with $[Rh(C_2H_4)_2Cl]_2$ as a precatalyst to assess whether **2a** could be obtained with improved conversions and in high enantioselectivity. Chiral diene ligands have been shown to provide excellent results in asymmetric 1,4-arylation reactions,[27,28,29] and in view of the success obtained with secondary amide-containing ligand **L1**[30] in our study of the asymmetric arylation of alkenyl heteroarenes,[4] this diene was evaluated first. Although **L1** did lead to **2a** in 97% ee, the conversion was only 35% (entry 2). Increasing the temperature to 120 °C did increase the conversion with only a slight impact upon enantioselection (95% ee), but appreciable starting material remained (entry 3). Additional amide-containing chiral dienes were then investigated. The enantioselectivity remained high with ligand **L2** that lacks the pyrrole on the cyclohexyl ring, but the conversion was low (entry 4). Ligand **L3**[4] containing a morpholine amide provided improved conversion (76%) at 80 °C, but the product was formed in only 70% ee (entry 5). Ligands **L4** and **L5** containing tertiary amides gave improved results (entries 6 and 7), with dibenzylamide-containing ligand **L5** giving the product in >95% conversion, 92% isolated yield, and 95% ee (entry 7). In contrast, ligand **L6** containing only one benzyl group on the amide nitrogen atom afforded inferior results (entry 8), further suggesting that under these conditions, a tertiary amide in the ligand is beneficial for high conversion. Finally, (*R*)-BINAP (**L7**) was tested for comparison, and although the enantioselectivity was high, the reaction did not go to completion (entry 9). On the basis of these results, ligand **L5** was selected for further study.

Next, the addition of a range of arylboronic acids to various alkenyl-*p*-nitroarenes was investigated (Table 2), and the enantioselectivity of the reaction was, in most cases, high (84–97% ee). In addition to a *p*-nitrophenyl group (entries 1–12),

Table 2 Catalytic asymmetric arylation of alkenyl-*p*-nitroarenes[a]



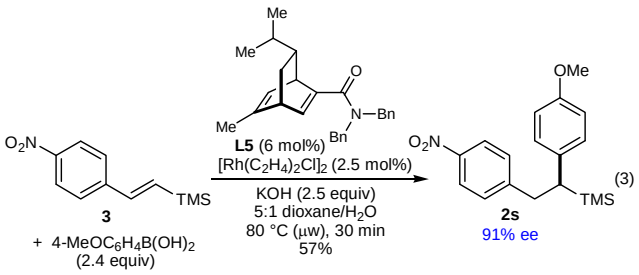
Entry	Product	Yield (%)	ee (%)	Entry	Product	Yield (%)	ee (%)	Entry	Product	Yield (%)	ee (%)
1	**2a**	92 (90)[b]	95 (94)[b]	7	**2g**	89	94	13	**2m**	0	—
2	**2b**	79	89	8	**2h**	81	94	14	**2n**	90	88
3[c]	**2c**	83	95	9	**2i**	83	93	15[e]	**2o**	79	87
4	**2d**	87	94	10	**2j**	74	92	16	**2p**	80	91
5	**2e**	90	92	11	**2k**	82	91	17	**2q**	85	92
6[d]	**2f**	61	97	12	**2l**	85	91	18	**2r**	54	84

[a] Unless otherwise stated, reactions were conducted using 0.20 mmol of **1a**–**1k**. Cited yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Values in parentheses refer to a reaction conducted under thermal heating under otherwise identical conditions. [c] Reaction performed using 1.0 mmol of **1b** at 80 °C under thermal heating for 1 h, using 2.5 mol% of Rh and 3 mol% of **L5**. [d] Reaction time was 1 h. [e] Reaction performed using 1.0 mmol of **1h**.

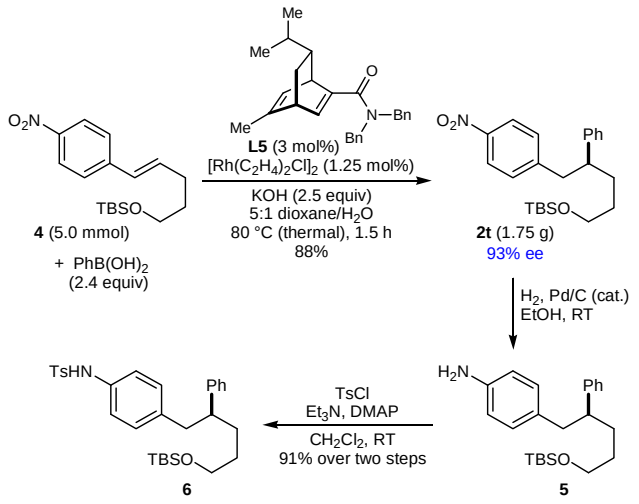
other arenes that provide effective activation in this process include *o*-fluoro-*p*-nitrophenyl (entry 14), *m*-methyl-*p*-nitrophenyl (entry 15), *m*-carbomethoxy-*p*-nitrophenyl (entry 16), and *p*-nitro-*m*-(trifluoromethyl)phenyl (entry 17). The reaction is not limited to alkenyl-*p*-nitrobenzenes; substrate **1k** containing a 4-nitronaphthyl group also underwent arylation to provide **2r**, though the yield and enantioselectivity were somewhat diminished with this sterically more demanding substrate (entry 18). The range of tolerated substituents at the β-position of the alkene include simple linear alkyl groups (entries 1–9 and 14–18), a cyclopropyl group (entry 10), an allyl ether (entry 11), and an allyl amine (entry 12). However, a β-aryl group was found to inhibit the reaction (entry 13). Regarding the scope of the nucleophile, arylboronic acids containing methyl, halogen, or methoxy substituents were competent reaction partners in this process. The reaction of sterically demanding 2-methylphenylboronic acid with substrate **1b** provided **2f** in 97% ee, though in a modest 61% yield (entry 6). Thermal heating is as effective as microwave heating, as evidenced by a reaction conducted under otherwise identical conditions (entry 1, values in parentheses). Furthermore, thermal heating was employed in the addition of phenylboronic acid to **1b** on a 1.0 mmol scale with

1.25 mol% of $[Rh(C_2H_4)_2Cl]_2$ and 3 mol% of **L5** at 80 °C for 1 h, which provided **2c** in 83% yield and 95% ee (entry 3).

An additional demonstration of reaction scope is provided in eq 3, where substrate **3** containing a β-trimethylsilyl substituent underwent arylation in 57% yield and 91% ee.[31]



To test the utility of this process further, a preparative-scale reaction was performed using substrate **4** (5.0 mmol) containing an oxygenated alkyl subsituent at the β-position (Scheme 1). This experiment provided **2t** in 88% yield and 93% ee. In addition, reduction of the nitro group of **2t**, followed by tosylation of the resulting amine **5**, provided sulfonamide **6** in 91% yield over two steps, the absolute stereochemistry of which was determined by single crystal X-ray analysis (Fig. 1).[32] The sense of enantioinduction observed using ligand **L5** is consistent with the stereochemical model proposed for previously reported examples of arylation of acyclic electron-deficient alkenes using structurally similar chiral dienes.[4,30] In this model, the rhodium–



Scheme 1 Larger-scale arylation of **4** and subsequent elaboration

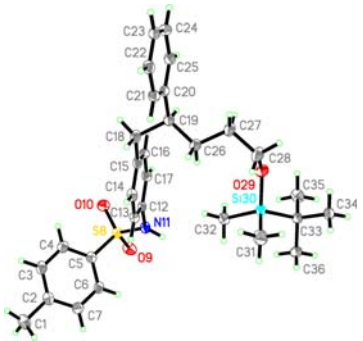


Fig. 1 ORTEP drawing of **6** with ellipsoids set at 50% probability

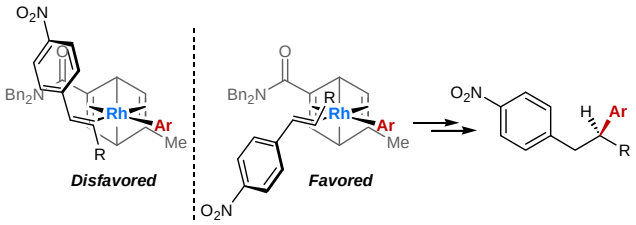
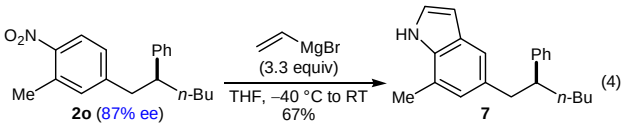


Fig. 2 Model for stereochemical induction

aryl bond is situated *trans* to the more electron-deficient alkene, and binding of the alkenylnitroarene occurs in a manner that minimizes unfavorable steric interactions (Fig. 2).

Nitroarenes are well-known to undergo a range of valuable reactions, making them versatile intermediates in the preparation of dyes, pharmaceuticals, and other functional compounds.[33] To demonstrate the synthetic utility of the arylation products described herein, **2o** was smoothly converted into indole **7** in 67% yield by treatment with vinylmagnesium bromide according to the method of Bartoli and co-workers (eq 4).[34,35]



Further experiments provided insights into the structural features required in the substrate for the reaction to proceed under the present conditions. Substrates **8** and **9** containing *m*-nitrophenyl and *o*-nitrophenyl groups, respectively, did not provide the desired arylation products (Fig. 3).

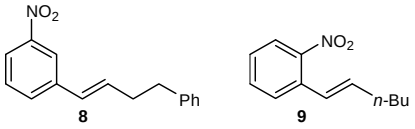
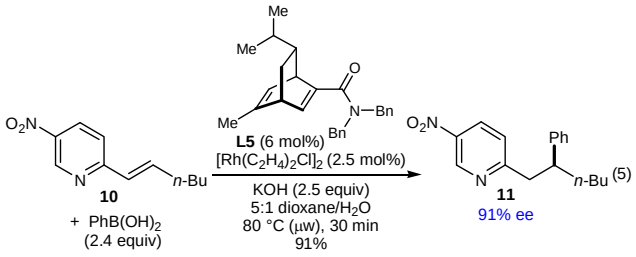


Fig. 3 Unreactive substrates

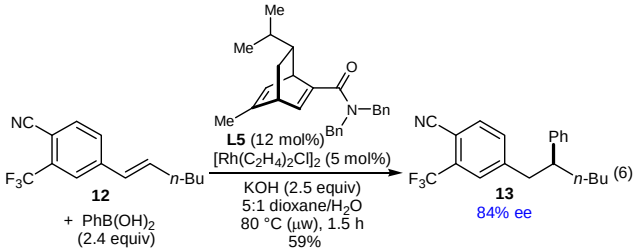
While the lack of reactivity of **8** is not surprising given that the nitro group is not conjugated with the alkene,[6d] the failure of **9** to undergo arylation was somewhat unexpected, given that *o*-nitrostyrene has been shown to react smoothly with a variety of active methylene compounds under basic conditions.[6d] Attempted arylation of **9** using a stoichiometric quantity of the rhodium–ligand complex also provided no evidence of the desired product, suggesting that the problem is one of reactivity rather than catalyst turnover. The addition of 10 mol% of substrate **9** to a repeat of the reaction of Table 2, entry 1 under otherwise identical conditions led to the formation of **2a** in >95% conversion and 94% ee, further suggesting that **9** does not poison the catalyst. Exactly how the *o*-nitro group in **9** inhibits the carborhodation step in the mechanism of rhodium-catalyzed addition of arylboronic acids to electron-deficient alkenes[36] is not known at this time.

Nevertheless, the powerful effect of a *p*-nitro group allowed us

to address a problem discovered during our recent study of enantioselective rhodium-catalyzed additions of arylboronic acids to alkenylheteroarenes, which identified a 2-pyridyl group as providing insufficient activation of an adjacent alkene for arylation to proceed efficiently.[4] Gratifyingly, 2-alkenylpyridine **10** containing a 5-nitro group underwent arylation in high yield and enantioselectivity (eq 5).



Finally, efforts to employ alkenylbenzene substrates containing a single *para*-electron-withdrawing substituent other than a nitro group, such as acetyl, nitrile, or methanesulfonyl, with only low conversions into mixtures of identified products being observed. However, substrate **12**, containing a *p*-cyano-*m*-(trifluoromethyl)phenyl group, did undergo arylation in 59% yield and 84% ee in the presence of 10 mol% of the rhodium–chiral diene complex after 1.5 h (eq 6).



In contrast, no reaction was observed using (*R*)-BINAP (**L7**) as the ligand. The result of eq 6 suggests that there is scope to increase the range of electron-deficient arenes that can be used as activating groups, and future developments in this area may rest upon the identification of more active catalysts and/or improved reaction conditions.

Conclusions

In summary, highly enantioselective rhodium-catalyzed additions of arylboronic acids to alkenyl-*p*-nitroarenes and an alkenyl-*p*-cyano-*m*-(trifluoromethyl)arene have been developed. These reactions represent, to the best of our knowledge, the first examples of catalytic asymmetric additions of air- and moisture-stable organometallic reagents to alkenes activated by electron-deficient arenes. Extension of this concept to other classes of reactions may present exciting new opportunities for asymmetric catalysis. Studies in this area are underway, and will be reported in due course.

Acknowledgements

This work was supported by a University of Edinburgh MTEM Scholarship. We thank Benoit Gourdet and Iain D. Roy for assistance in the preparation of ligands, and Dr. Fraser J. White for assistance with X-ray crystallography. We are grateful to the EPSRC for the award of a Leadership Fellowship to H. W. L. We also thank the EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea, for providing high resolution mass spectra.

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